THE STRUCTURE OF GOSSYPOLIC ACID

BY

JOHN THOMAS FITZPATRICK

S.B., Harvard College, 1938

M.S., University of Illinois, 1939

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY IN THE GRADUATE SCHOOL OF THE UNIVERSITY OF ILLINOIS, 1941

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THE STRUCTURE OF GOSSYPOLIC ACID

INTRODUCTION

Gossypol has been postulated by Adams and co-workers [1] to be 2,2′-bi-(1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl). The only remaining point of uncertainty in this formulation is the relative positions of the binaphthyl linkage and the methyl groups. Gossypolic acid, first isolated by Karrer and Tobler [2] from the ozonization of gossypol acetic acid, is believed to have the structure 2,2′-dihydroxy-3,3′-dicarboxy-4,4′-diisobutyryl-6,6′-dimethylbiphenyl. It is the only gossypol derivative in which the outer rings are destroyed, while the inner rings are left intact. This investigation was undertaken in an effort to prove its structure.

DISCUSSION OF RESULTS

Gossypolic acid could not be obtained by ozonization of gossypol acetic acid in any solvent but glacial acetic acid, nor by ozonization of gossypol, anhydrogossypol, or gossypol hexamethyl ether in any solvent tried.

Decarboxylation of gossypolic acid and methylation of the product resulted in a dimethyl ether, presumably 2,2′-dimethoxy-4,4′-diisobutyryl-6,6′-dimethylbiphenyl. Several unsuccessful syntheses of this compound were undertaken.

The Ullman reaction failed to produce any properly substituted biphenyl when attempted on 3-methyl-4-bromo-5-nitrobenzonitrile, methyl (3-methyl-4-bromo-5-nitrobenzoate),[3] and 2-iodo-3-methyl-5-carboxybenzenesulfonic acid. The latter compound was prepared by sulfonation of 3-methyl-4-aminobenzoic acid, and subsequent replacement of the amino group with iodine. A synthesis of 3-methyl-4-iodo-5-nitrobenzonitrile paralleling Teeter's method [3] for the bromo compound failed when it was found that 3-methyl-4-iodoaniline could not be converted to 3-methyl-4-iodobenzonitrile.

Likewise unsuccessful were attempts to produce biphenyl derivatives by reduction of the diazonium salt of 2-amino-3-methyl-5-carboxybenzenesulfonic acid by Atkinson's method,[4] and by reduction of 3-nitro-5-methylanisole to the hydrazo compound, either with zinc and alkali or catalytically, and subsequent benzidine rearrangement.

Replacement of the amino group in 2-amino-3,5-dimethylanisole with bromine, followed by an Ullman reaction, produced 2,2′-di-

methoxy-4,6,4′,6′-tetramethylbiphenyl. Attempts were unsuccessful to oxidize this compound to 2,2′-dimethoxy-4,4′-dicarboxy-6,6′-dimethylbiphenyl, 2-nitro-3,5-dimethylanisole to 3-methyl-4-nitro-5-methoxybenzoic acid, or 2-bromo-3,5-dimethylanisole to the corresponding bromo acid. An x-iodo-3,5-dimethylanisole, prepared by mercuration of 3,5-dimethylanisole and subsequent replacement with iodine, could not be oxidized to the corresponding monobasic acid.

The introduction of an isobutyryl group into the position *para* to the amino group either in *o*-toluidine or in 2-amino-3- methylanisole could not be accomplished.

Bromination of 3-methyl-5-hydroxybenzoic acid, the corresponding 5-methoxy acid, 3-methyl-5-nitrophenol, and the corresponding methyl ether in every case gave either no reaction at all or such a mixture of products as to be useless as a synthetic method.

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VITA

The writer was born in Salt Lake City on October 13, 1918. He attended the public schools of that city, and in June, 1934, he was graduated from East Salt Lake High School. He attended the University of Utah from 1934 to 1936, and Harvard College from 1936 to 1938. He received the degree of Bachelor of Science from the latter institution in June, 1938. In September of that year he entered the Graduate School of the University of Illinois, receiving the degree of Master of Science in June, 1939. During the year 1940-41 he held the Solvay Process Company Fellowship.